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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/436,347	11/09/1999	CHRISTINE A. WHITE	012712-643	6491

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EXAMINER	
HARRIS, ALANA M	

ART UNIT	PAPER NUMBER
1642	4

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/436,347	WHITE ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 August 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. Claims 1-18 are pending.

Claims 1, 8, 11 and 12 have been amended.

Claims 13-18 have been added.

Claims 1-18 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections

Specification

3. Applicants have amended the specification to properly reflect the use of trademarks RITUXAN®, PRIMATIZED® and RITUXIMAB® .

4. The disclosure is no longer objected to because the specification:

(a) lists the correct address of the American Type Culture Collection;

(b) contains properly identified trademarks; and

(c) no longer contains embedded hyperlinks or other forms of browser-executable code.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

5. The rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention is withdrawn in light of Applicants' arguments.

6. The rejection of claims 1-12 under 35 U.S.C. 112, second paragraph, listed as sections a-c and e-g on pages 10 and 11 of the first action on the merits as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicants' arguments.

Claim Rejections - 35 USC § 103

7. The rejection of claims 1, 5, 6 and 9 under 35 U.S.C. 103(a) as being unpatentable over Ford and Donegan (Highlights in Oncology Practice 16(2): 40-50, 1998) and Maloney et al. (Blood 90(6): 2188-2195, 1997) is withdrawn.

8. The rejection of claims 1, 8 and 10 under 35 U.S.C. 103(a) as being unpatenable over either Ford and Donegan (Highlights in Oncology Practice 16(2): 40-50, 1998) or Maloney et al. (Blood 90(6): 2188-2195, 1997), in view of Hudziak et al. (U.S. Patent # 5,677,171; 1997) is withdrawn.

9. The rejection of claims 1, 8 and 10 under 35 U.S.C. 103(a) as being unpatenable over either Ford and Donegan (Highlights in Oncology Practice 16(2):40-50, 1998) or Maloney et al. (Blood 90(6):2188-2195, 1997), in view of Hudziak et al. (U.S. Patent # 5,677,171; 1997) is withdrawn.

Maintained Rejections and New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. The rejection of claim 7 under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials is maintained.

Applicants assert the specification has been amended to reference the ATCC number assigned to the deposit and that restriction on public access were irrevocably withdrawn upon issuance of U.S. Patent 5,736,137. These points of view have been considered but found to be unpersuasive.

The Examiner has reviewed the specification and has not found the reference to the ATCC number assigned to the alleged deposit. Remiss from the instant application is evidence of the public availability of the claimed antibody or evidence of the reproducibility without undue experimentation of the claimed antibody. There needs to be assurance in the instant case that the deposit is made under the provisions of the Budapest Treaty and that the deposits comply with the criteria set forth in 37 CFR

1.801-1.809 regarding availability and permanency of deposits. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record that has the authority.

11. The rejection of claims 1-12 and 14-17 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained and made.

a. The recitation "high numbers" as listed in claims 1, 12 and 14 is indefinite. Applicants argue "...this phrase must be read in the context of a hematological malignancy" and "...has a well understood meaning to those familiar with hematological disorders". This argument has been carefully considered and found unpersuasive. The metes and the bounds of the claimed invention still cannot be determined. There is no reference point as to what to base the high number on. It is not clear within what range high numbers should be assessed.

Claim Rejections - 35 USC § 102

12. The rejection of claims 1, 2, 4, 6-9 and 11-17 under 35 U.S.C. 102(b) as being anticipated by Maloney et al. (Blood 90(6): 2188-2195, 1997) is maintained and made.

Applicants argue the Examiner is of the opinion that the instant reference reads on the claimed invention and in view of the clarification of the term, high numbers the reference does not read on the claims. These points of view have been considered, but found unpersuasive.

The chimeric monoclonal antibody (MoAb), IDEC-C2B8 art known as rituximab has antitumor activity in patients with non-Hodgkin's lymphomas, a hematologic malignancy associated with high numbers of circulating tumor cells that is refractory to chemotherapy in combination with the chemotherapeutic agent, prednisone, see Abstract. This activity clearly reflects that the MoAb was administered in an amount effective for four weeks to achieve a reduction in circulating tumor cells, see page 2189, column 1, last full paragraph. Patients were treated with a 375mg/m^2 dose for four weeks, see page 2189, column 1, Materials and Methods section. This dosage is within the range of Applicants'.

13. The rejection of claims 1-4, 7 and 11-17 under 35 U.S.C. 102(a) as being anticipated by Ford and Donegan (Highlights in Oncology Practice 16(2):40-50, 1998) is maintained and made.

Applicants argue that Ford does not disclose a method of treating CLL with RITUXAN®, alone or in combination with other therapies and with regard to CLL it is non-enabling. Applicants are also of the opinion that Ford simply reports only non-enabling disclosure concerning the possible treatment of CLL. These arguments have been found unpersuasive.

Ford clearly discloses a method of treating hematologic malignancies, B-cell lymphoma, CLL and prolymphocytic leukemia, see page 44, column 2, Single-Agent Studies section; page 47, column 1, end of bridging paragraph. All of these hematologic malignancies are associated with high numbers of circulating tumor cells. Table 1 evidences the administration of rituximab (RITUXAN®; formerly IDEC-C2B8), to patients with relapsed lymphoma. The claimed antibody was administered weekly for about 2 to 10 weeks in combination with chemotherapy, the same as that claimed. The

rituximab was combined with cyclophophamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy. It is reasonable to conclude that with the administration of the rituximab the method of avoiding or reducing the toxicity associated would occur simultaneously.

Claim Rejections - 35 USC § 103

14. Claims 1-7 and 9-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ford and Donegan (Highlights in Oncology Practice 16(2):40-50, 1998).

Applicants argue that Ford and Donegan report only non-enabling disclosure concerning the possible treatment of CLL. This argument has been considered but found unpersuasive for the reasons stated above.

The teachings of Ford have been presented above. Ford does not teach the administration of the antibody in the specific dosages and time points as set forth in claims 5, 9 and 18.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the anti-CD20 antibody in the recited dosages at the designated time points. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that the dosages of any therapeutic agent must be adjusted and optimized.

15. Claims 1, 2, 4-9 and 11-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maloney et al. (Blood 90(6): 2188-2195, 1997).

Applicants argue that Maloney excludes patients with high numbers of circulating tumor cells. This argument has been considered but found unpersuasive for the reasons stated above.

The teachings of Ford have been presented above. And in view of the indefiniteness of the phrase "high numbers" the Ford reference is anticipatory. However, Ford does not teach the administration of the antibody in the specific dosages and time points as set forth in claims 5, 9 and 18.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the anti-CD20 antibody in the recited dosages at the designated time points. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings well known in the art, that the dosages of any therapeutic agent must be adjusted and optimized.

16. Claims 1-4, 7, 8 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatenable over Ford and Donegan (Highlights in Oncology Practice 16(2):40-50, 1998), in view of Hudziak et al. (U.S. Patent # 5,677,171, October 14, 1997).

Applicants argue that Ford does not anticipate the claimed method and Hudziak administers cytokines for reason different from that of Applicants. For the reasons of record this argument is found unpersuasive.

The teachings of Ford have been presented in the 102a rejection. Ford does not teach the disclosed method with the administration of a lymphokine. Albeit, Hudziak

uses the cytokines for a reason contrary to Applicants, intrinsically the administration of the cytokines would upregulate the CD20 molecules on the surface of the tumor cells in order to enhance the effects of the therapeutic anti-CD20 antibody. Accordingly, it follows Hudziak teaches the simultaneous administration of therapeutically effective amount of antibodies and a therapeutically effective amount of a cytotoxic factor, such as TNF-alpha. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to administer a combination of a lymphokine, such as TNF-alpha and the claimed anti-CD20 antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Hudziak that a cytotoxic factor, such as TNF-alpha exerts it cytostatic (cell growth suppressive) and cytotoxic (cell destructive effect) towards circulating malignant tumor cells of B-PLL or CLL.

17. Claims 1, 2, 4, 6-9 and 11-17 are rejected under 35 U.S.C. 103(a) as being unpatenable over Maloney et al. (Blood 90(6): 2188-2195, 1997), in view of Hudziak et al. (U.S. Patent # 5,677,171, October 14, 1997).

Applicants' arguments in regard to Maloney have been presented, as well as the argument that Hudziak administers cytokines for reason different from that of Applicants. For the reasons of record this argument is found unpersuasive.

The teachings of Maloney have been presented in the 102b rejection. Maloney does not teach the disclosed method with the administration of a lymphokine. Albeit, Hudziak uses the cytokines for a reason contrary to Applicants, intrinsically the

administration of the cytokines would upregulate the CD20 molecules on the surface of the tumor cells in order to enhance the effects of the therapeutic anti-CD20 antibody. Accordingly, it follows Hudziak teaches the simultaneous administration of therapeutically effective amount of antibodies and a therapeutically effective amount of a cytotoxic factor, such as TNF-alpha. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the claimed invention to administer a combination of a lymphokine, such as TNF-alpha and the claimed anti-CD20 antibody. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by teachings of Hudziak that a cytotoxic factor, such as TNF-alpha exerts it cytostatic (cell growth suppressive) and cytotoxic (cell destructive effect) towards circulating malignant tumor cells of B-PLL or CLL.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 7:00 am to 4:30 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Alana M. Harris, Ph.D.
September 2, 2003